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Wotherspoon, A. C., Young, I. S., McCance, D. R., Patterson, C. C., Maresh, M. J. A., Pearson, D. W. M., Walker, J. D., & Holmes, V. A. (2016). Serum Fatty Acid Binding Protein 4 (FABP4) Predicts Pre-eclampsia in Women with Type 1 Diabetes. *Diabetes Care*, *39*(10), 1827-1829. https://doi.org/10.2337/dc16-0803

Published in:
Diabetes Care

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Download date:05. May. 2023

Serum Fatty Acid Binding Protein 4 (FABP4) Predicts Pre-eclampsia in Women with Type 1 Diabetes

Running Title: FABP4 Predicts Pre-eclampsia

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Word Count: 1,346 including abstract subheadings (Limit 1,350)

Number of Tables: 1

Number of Figures: 0

Abstract

Objective

To examine the association between Fatty Acid Binding Protein 4 (FABP4) and pre-eclampsia risk in women with type 1 diabetes.

Research Design and Methods

Serum FABP4 was measured in 710 women from the DAPIT study in early pregnancy and in the second trimester (median 14 and 26 weeks gestation, respectively).

Results

FABP4 was significantly elevated in early pregnancy (geometric mean [interquartile range]: 15.8ng/ml [11.6-21.4] vs. 12.7ng/ml [9.6-17]; *P*<0.001) and the second trimester (18.8ng/ml [13.6-25.8] vs. 14.6ng/ml [10.8-19.7]; *P*<0.001) in women who later developed pre-eclampsia. Elevated second trimester FABP4 was independently associated with pre-eclampsia (OR 2.87 (95%CI 1.24, 6.68), P=0.03). Addition of FABP4 to established risk factors significantly improved Net Reclassification Improvement at both time-points and Integrated Discrimination Improvement in the second trimester.

Conclusions

Increased second trimester FABP4 independently predicted pre-eclampsia and significantly improved reclassification and discrimination. FABP4 shows potential as a novel biomarker for pre-eclampsia prediction in women with type 1 diabetes.

Word Count: 153 including subheadings (limit 150)

Introduction

Pre-eclampsia, defined as new onset hypertension and proteinuria occurring after 20 weeks gestation, is associated with significant perinatal morbidity and mortality(1, 2). Women with type 1 diabetes are 2 to 4 more times more likely develop pre-eclampsia than the background population(3, 4).

Fatty Acid Binding Protein 4 (FABP4), or adipocyte fatty acid binding protein, is an intracellular lipid chaperone involved in co-ordination of lipid transportation(5). FABP4 is expressed mainly in adipocytes and can be released into the circulation(6). In the non-pregnant state FABP4 is associated with known pre-eclampsia risk factors: obesity, hypertension and diabetes(6, 7).

Several studies have reported elevated FABP4 in women with pre-eclampsia(8, 9) or who later developed pre-eclampsia(10), compared to those who did not, although all studies excluded women with diabetes.

Our objective was to examine the role of FABP4 as a potential biomarker for pre-eclampsia alone, and in tandem with established clinical risk factors, in women with type 1 diabetes.

Research design and Methods

The population comprised 710 of the 762 women from the Diabetes and Pre-eclampsia Intervention Trial (DAPIT), a randomized multicenter double-blind placebo-controlled trial investigating vitamin C and E supplementation and risk of pre-eclampsia in women with type 1 diabetes(11). Pre-eclampsia, the primary endpoint, was defined using International guidelines(1, 12). Women provided written

informed consent. West-Midlands Multicenter Research Ethics Committee approved the study (MREC 02/7/016).

Blood samples were collected at randomization (8-22 weeks; median 14 weeks) and in the second trimester (median 26 weeks). Serum samples were batch-analyzed, blind to pre-eclampsia status, using a commercially available ELISA (Biovendor, Modrice, Czech Republic). Inter-assay and intra-assay CVs were 8.3% and 3.8%, respectively.

Intervention and control groups were analyzed together as supplementation did not reduce pre-eclampsia risk (risk ratio: 0.81; 95% CI: 0.59, 1.12, *P*=0.20)(11); FABP4 levels were not different between groups, and the effect of supplementation on pre-eclampsia risk did not depend on FABP4.

Statistical analysis

FABP4 concentrations were positively skewed and therefore logarithmically transformed. Values are reported as geometric mean and interquartile range (IQR). Chi-squared (X^2) and independent samples *t*-tests were used for group comparisons. Logistic regression analysis investigated the association between FABP4 and pre-eclampsia before and after adjusting for the following risk factors: age, BMI, gestational age, blood pressure, parity, duration of diabetes, smoking status, history of pre-eclampsia, $HbA_{1c,}$ renal status, and DAPIT treatment group. The area under the receiver operating characteristic curve (AUROC) was used to assess the predictive value of FABP4 for pre-eclampsia(13). Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) indices were calculated to determine the clinical utility of the addition of FABP4 to established risk factors and the ability of FABP4 to improve pre-eclampsia prediction (for calculation

AUROC, NRI and IDI, see Supplementary Data)(14). Statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY), Stata release 14 (StataCorp, College Station, TX) and the Hmisc package in R version 3.1.3 (R Core Team, Vienna, Austria).

Results

Serum from one or both time-points was available for 710 women, of whom 120 (17%) developed pre-eclampsia (for maternal and clinical characteristics see Supplementary Table 1).

FABP4 levels at randomization (median 14 weeks) and 26 weeks were significantly higher in women who later developed pre-eclampsia compared with those who did not (Table 1). Of the 319 women with blood samples at 13 weeks or less, FABP4 levels were elevated in those who later developed pre-eclampsia compared to those who did not (*P*=0.02).

For each doubling of serum FABP4, adjusted risk of pre-eclampsia increased by 40% (OR 1.4 (95%CI 1.0, 2.0), P=0.031) and 60% (1.6 (1.1, 2.3), P=0.017) at 14 and 26 weeks, respectively. The independent ability of FABP4 to predict preeclampsia, in relation to quarters of FABP4 in combination with established risk factors, is shown in Supplementary Table 2. In the second trimester, the highest quarter of FABP4 was a significant independent predictor of pre-eclampsia compared with the lowest (OR 2.87; 95%CI 1.24, 6.68), P=0.03).

AUROCs for FABP4 alone were 0.622 and 0.646 at 14 and 26 weeks, respectively (Table 1). When FABP4 was added to the model containing established risk factors,

AUROCs were 0.801 and 0.825 at 14 and 26 weeks, respectively (both non-significant from established risk factors alone).

The NRI statistic showed that the addition of FABP4 to established risk factors significantly increased correct reclassification of cases and non-cases at both 14 and 26 weeks. The IDI statistic showed that FABP4 significantly increased discrimination between cases and non-cases in the second trimester (Table 1).

Conclusions

We believe this is the first study to date to investigate FABP4 levels in relation to development of pre-eclampsia and to investigate its clinical utility in pregnant women with type 1 diabetes. Maternal FABP4 levels were significantly elevated in women who later developed pre-eclampsia compared with those who did not both at 14 and 26 weeks gestation. Furthermore, the addition of FABP4 to established risk factors improved the reclassification index at both time-points and discrimination index in the second trimester.

Only one previous study has measured FABP4 prior to the onset of pre-eclampsia. In line with our findings, Scifres and colleagues(10) reported significantly elevated FABP4 before 13 weeks and at 26 weeks gestation in non-diabetic women who later developed pre-eclampsia.

FAPB4 may play a role in pre-eclampsia development. Shangguan and colleagues(9) reported increased third trimester FAPB4 levels in women with pre-eclampsia compared with healthy pregnant and non-pregnant women, suggesting no effect of pregnancy on FABP4, thus implicating FABP4 in pre-eclampsia development.

This study explores the both predictive properties and clinical utility of FABP4 in relation to pre-eclampsia in women with type 1 diabetes. FABP4 remained significantly associated with pre-eclampsia after controlling for established risk factors. FABP4, when added to established risk factors, did not significantly increase the AUROC. However, the NRI and IDI indices, which are proposed as superior methods to determine clinical utility of a biomarker(14), showed that FABP4, in addition to clinical risk factors, improved the prediction of pre-eclampsia. This was significant for NRI at 14 weeks and for both NRI and IDI at 26 weeks.

The strengths of this study include the study size, with DAPIT being the largest prospective dataset reported of thoroughly characterized women with type 1 diabetes, together with the strict definition of pre-eclampsia, as each potential case was reviewed independently by three clinicians(11, 15). In addition, women with essential hypertension or any existing renal disease were included, making our study more representative of the typical population. The study has the limitation that trial participants may not be entirely representative of all pregnant women with type 1 diabetes, as they were self-selecting. Randomization samples also represented a range of gestational ages from 8 weeks to 22 weeks.

In summary, we believe this is the first study to investigate FABP4 in relation to the development of pre-eclampsia in pregnant women with type 1 diabetes. FABP4 levels in both the first and second trimester were significantly associated with the development of pre-eclampsia. Elevated second trimester FABP4 independently predicted pre-eclampsia, significantly improving reclassification and discrimination. While further studies are now needed to replicate these findings, our data suggest that FABP4 shows potential as a novel biomarker for pre-eclampsia prediction in women with type 1 diabetes.

Acknowledgements

This study was funded by grants 067028/Z/02/Z and 083145/Z/07/Z from The Wellcome Trust (registered charity number 210183) and from the Department of Employment and Learning, Northern Ireland. A.C.W. carried out laboratory analysis, researched and wrote the manuscript. I.S.Y., D.R.M., C.C.P., M.J.A.M., D.W.M.P, J.D.W and V.A.H reviewed and edited the manuscript. C.C.P. also supervised the statistical analysis. No potential conflicts of interest relevant to this article were reported. V.A.H. is the guarantor of this work and as such, had full access to all the data and the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Parts of this study have been accepted for presentation at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, 10-14th June 2016.

The authors thank Cyril McMaster from the Centre for Public Health, Queen's University Belfast, United Kingdom, for his assistance with laboratory analysis, the patients who took part in the DAPIT study, the DAPIT research midwives who collected the data and the collaborators at each center.

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Table 1:

Serum FABP4 concentrations at randomization and in the second trimester, with area under the receiver operating characteristic curve (AUROC), Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) analyses

	Maternal serum FABP4 concentration* (ng/ml)		Area under receiver operating characteristic curve (AUROC)				NRI (*P*)	IDI (*P*)
	Pre-eclampsia	No pre-eclampsia	FABP4 alone	Established risk factors without FABP4	Established risk factors with FABP4	Incremental area (*P*)†		
Randomization	15.8 (11.6-21.4)	12.7 (9.6-17.0)	0.622	0.793	0.801	0.008 (0.17)	0.306 (0.003)	0.009 (0.11)
Second trimester	18.8 (13.6-25.8)	14.6 (10.8-19.7)	0.648	0.819	0.825	0.006 (0.34)	0.251 (0.02)	0.012 (0.048)

*Reported as geometric mean and interquartile range

† Comparison of AUROCs: Established risk factors without FABP4 vs Established risk factors with FABP4